PR

3885

OTS: 60-31,756

JPRS: 3885

15 September 1960

IONIZING RADIATIONS AND THE HUMAN ORGANISM:

THE SEARCH FOR MEANS OF PROTECTION AGAINST RADIATION CONTAMINATION

- USSR -

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Distributed by:

OFFICE OF TECHNICAL SERVICES
U. S. DEPARTMENT OF COMMERCE
WASHINGTON 25, D. C.
Price: $0.50

U. S. JOINT PUBLICATIONS RESEARCH SERVICE
205 EAST 42nd STREET, SUITE 300
NEW YORK 17, N. Y.

F O R E W O R D

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JPRS: 3885

CSO: 4202-D

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[Following is a translation of an article by Professor B. N. Tarusov in the Russian-language periodical Priroda (Nature), Moscow, Vol. 49, No. 3, March 1960, pages 33-38.]

Progressive scientists the world over are working intensively to develop effective measures for protecting the human organism against penetrating radiation. Projects are being pursued on an extensive scale with regard to so-called chemical protection or prophylaxis -- utilization of the property of some chemical substances, when introduced prior to irradiation, to abate radiation contamination.

The well-known Belgian scientist, Academician Z. M. Bacq, and others, consider that the mechanism of prophylactic protection can be explained on the basis of a theory of indirect radiation effect. [see Note]. Other investigators (B. N. Tarusov and others) deem that an important part in radiation contamination is played by radio-chemical reactions originating in the organic substances of cell and tissue, and that this brings about the protective effect. The present article examines the principle theses of this research. [Note: See Priroda, No. 9, 1959, pages 33-38.]

The Mechanism of Radiation Contamination

Due to their high radiochemical activity, nuclear radiations have a strongly destructive effect upon organisms. Their destruction, particularly of the highest ones, is brought about by even negligibly small doses of radiation energy. It has been computed that no more than one ten-billionth of all the molecules contained in the living cells of an organism need be directly affected for that organism to be destroyed. In distinction from ultraviolet and the other types of radiation, absorption of the nuclear radiations depends not on the molecular structure of a substance, but merely on its atomic weight which, for the majority of elements comprising the molecules of living cells, is more or lessuniform and comparatively low.

In the course of the interaction of radiation energy with the tissues of an organism, chemical reactions arise which, after a single act of direct irradiation, draw into the process of contamination an enormous number of molecules. The degree of contamination is so great that it leads to disruption of the coordinated interrelationship of the various metabolic processes of the organims, and then to its general breakdown.

Chain Reactions After Radiation Action

Active chemical products, formed during the act of direct irradiation, are the reason for the development of reactions with high ion yields.

Judging by the nature of their development, these primary radiochemical reactions in the cells and tissues of organisms belong to the so-called type of chain reaction. A characteristic feature of such reactions is the fact that they develop with continuous acceleration, and at first, while their rate of growth is small, they are difficult to detect. A principal role in the origin of chain reactions is played by highly active radicals, peroxides, and ions, possessing great energy, which originate under the influence of radiation. The theory of these reactions, which play a large role in various fields of chemistry, has, as is well known, been developed by Academician N. N. Semenov. The active products originating in the first stage are capable of evoking forms of molecular decomposition in which the same active products are formed again (regenerated). Therefore the process can develop continuously, repeating itself after brief direct irradiation. As a result of the development of such chains, the initially insignificant damage increases and leads to radiation sickness. Direct proof exists that, with the action of ionizing radiations on the tissue of an organism, chemically active radicals form in it; they have been detected in amino acids and albumins by direct methods of paramagnetic resonance [see Note 1]. The appearance of free radicals in yeast cells has been established at low temperatures. At the present time, a rather large number of experiments has already been carried out showing that, after irradiation, organic peroxide compounds form in animal tissues; these peroxide compounds, which are chemically highly active, can cause chain oxidation reactions [see Note 2]. It is possible to interrupt the development of radiation contamination and, consequently, of the radiochemical reactions, if these free radicals and peroxides are bound and rendered harmless. (Note 1: See Biofizika [Biophysics], Vol. 3, No. 1, 1958, p. 87.) (Note 2: See Voprosy Pitaniya [Problems of Nutrition], No. 4, 1958, pp. 60-64.)

Chemical Protection

Already in the 1940's it became known that some sulfur-containing compounds (cysteine, glutathione, thiourea) protect albumin against coagulation when it is acted upon by x-rays. It was soon established that, when added to bacterial cultures (immediately prior to irradiation), these same compounds raise the survival factor [vyzhivayemost'] of the cultures. It was also established that, when introduced into animals immediately prior to irradiation, these compounds increase the animals' resistance. This so-called prophylactic effect attracted scientists' attention. Besides cysteine and glutathione, the prophylactic effect is also attained through the use of other sulfur-containing compounds. Prophylactic action has been shown also by many amino compounds -- histamine, methylamine, tryptamine [triptamin], sulfothonine [serotonin], some cyano-compounds [nekotoryye tsianistyye soyedineniya], and compounds from the morphine group. It has turned out that many natural organic compounds, for instance adrenaline, some antibiotics -- aureomycin, tetracyclene [tetratsiklin] -- also afford protective action in case of irradiation. Considerable attention has been attracted by the preparation β-mercaptoethylamine, proposed by Z. M. Bacq; its effectiveness has been found to be higher than that of the other compounds.

The Role of Oxygen

Along with this, it has been established that reduction of the oxygen pressure, i.e., creating in the tissues and cells of the organism an insufficiency of oxygen (anoxia), exerts during irradiation a protective effect of the same order as with employment of the above-indicated chemical prophylactic measures. The English researchers J. Grey and K. Petersen have established that some substances, which influence the respiratory centers in the brain and retard their action, in this manner create a tissue anoxia and at the same time exert a protective effect. Some researchers have shown, on the basis of bacteria, that with the development of anoxia neither cysteine nor β-mercaptoethylamine will increase the protective effect. With reduction of the oxygen pressure to the level of the maximum protective effect, both cysteine and β-mercaptoethylamine become inactive and evoke no supplementary augmentation of the protective effect. This indicates that the action of protective chemical compounds and the protective effect of anoxia have something in common.

Direct and Indirect Effect

Grounds exist for supposing that the action of protective substances consists in the suppression of oxidation processes evoked in the tissues by radiation. According to the prevailing theory of indirect effect, the biological effect of ionizing radiation consists in the fact that under its influence, active radicals and hydrogen peroxide form in the water constituent of the tissue cells of the organism. In connection with this, Z. M. Bacq has proposed the hypothesis that the action mechanism of prophylactic substances can be reduced to a suppression of this process. In the various radiochemical reactions which take place in dilute aqueous solutions, water radicals and their peroxides play a considerable part. However, with a rise in the concentration of organic substance to 10% and above, the part played by the water radicals and peroxides diminishes sharply, and there begins to predominate the so-called direct effect, in which the decisive part in radiation contamination is played by the radicals and peroxides forming in the substance itself.

The indirect-effect theory completely fails to take into account the fact that the substances of which cells are built (albumins, carbohydrates, fats) are also susceptible to radiation: under its influence, active organic radicals and peroxides originate in these substances. Experiments have disclosed that when fatty substances (biolipids) are irradiated, 80 times the quantity of active peroxides is formed in them, as under the same conditions in water. With the action of radiations on aqueous solutions of high-molecular-weight polymer compounds (meta-acrylates), there takes place polymerization (the formation of high-molecular-weight compounds), which is connected with water radicals. Z. M. Bacq and B. Alexander [see Note] have shown that a certain interdependence exists between the ability to protect a model from polymerization and the ability to protect an animal under irradiation. However, the correspondence is far from complete. For example, cyano-compounds and certain aminos, which provide a protective effect for animals, do not manifest this effect on the described physico-chemical models. (Note: Cf. Z. Bacq, B. Alexander. Fundamentals of Radiobiology, 1955.)

The Protective Effect of Antioxidants

The supposition has been expressed by us that such a divergence between the protective effect observed in the case of aqueous models, and that pertaining to animals, is explained by the fact that active oxidizing radicals and peroxides are formed not only in water, and that not only they determine the development of radiation contamination. Many investigations have by now been published, wherein it is established that chemical protection against ionizing radions can be effected on dry objects as well. Observations by the scientist Falenter [?] of spores of the bacteria Bacillus Subtilis, thoroughly desiccated at high pressure in a vacuum [sic! -- probably should read "at high temperature in a vacuum" -- translator], show that reduction of the oxygen pressure during irradiation exerts the same kind of protective effect on these spores as on normal living organisms. The addition of protective substances to high-molecular-weight polymer compounds in a completely dry state protected them from destruction by ionizing radiations. Other scientists have, however, noted that in some cases increasing from 5% to 10% the quantity of water in wheat seeds not only does not augment, but on the contrary diminishes their sensitivity.

The protective effect of oxygen insufficiency is an indication of the fact that oxidation reactions, of a nature unusual for normal metabolism, arise in the cell and tissue substances of organisms. It has also been established that the majority of substances affording a protective effect possess one common property: they retard the development of oxidizing reactions. According to their properties, prophylactic substances are antioxidants which bind the free radicals and thus restrict the possibility of the development of chain reactions. These reactions develop in fatty substances (lipids) which play an important part in cell structures and in nucleotides and, possibly, in some of the other component substances of a cell.

The antioxidant effect of a substance depends on its ability to bind the intermediate products of oxidizing reactions, which are very complex, and in this manner to cut off their development. The intermediate products, a reduction in whose activity evokes inhibition and a breakoff of the chain reaction, vary as to their characteristics, therefore the selection of antioxidants also varies with different kinds of tissue. Not all substances which, for instance, possess reducing properties will also manifest antioxidant effects. At some substrata, oxidation reactions are inhibited by substances which oxidize.

There are many instances where the very same substance, acting upon substrata with nearly like properties, will in one case inhibit an oxidation reaction and in another reinforce it. Aniline, for instance, inhibits an oxidation reaction in oleic acid and activates it in linoleic acid.

Research, carried out on animal-tissue lipids and on various fats, has shown that the correlation (interdependence) between the ability of compounds to inhibit chain oxidation reactions, and their ability to exert a prophylactic effect, is much more complete than in the case of models where the principal role is played by water radicals.

Reduction of the oxygen content retards the development of oxidation reactions in case of the direct and the indirect effect of radiation, on lipid models and on models where this effect is brought about by water radicals; in accordance with this, it protects the organism against ionizing radiations. It has been shown that a protective effect is manifested, for organisms capable of enduring high oxygen concentrations (yeast [see Note]), not only with a reduction in the concentration of oxygen but also with its increase above 300 mm (Figure 1). This phenomenon is not reproducible in aqueous models. With an increase in oxygen pressure, the formation of peroxide solutions in water increases continuously and attains saturation. In a lipid model, the formation of organic peroxides under radiation is inhibited both with a reduction in the oxygen pressure, and with its increase over a certain threshold. This phenomenon may be explained by the characteristic features of oxidation reactions which take place in accordance with the chain mechanism. It has been established by Academician N. N. Semenov and his pupils that in oxidation reactions of this type, which are accompanied by chain ramification, inhibition is noted both for a decrease and for an increase in the oxygen pressure (upper- and lower limit). (Note: See Biofizika (Biophysics), Vol. 3, No. 1, 1958.)

Antioxidant activity with respect to lipids is characteristic to a majority of the compounds which manifest a prophylactic effect: this compounds (cysteine, β-mercaptoethylamine, thiouronic compounds, etc.), many amino compounds, phenols, etc. However, there are some compounds which do not seem to fit into this scheme. It has, for instance, been noted that a prophylactic effect is manifested by cyano-compounds [see Note 1]. However, they do not in a direct sense act as antioxidants and do not retard the formation of peroxides in water and in pure lipids. Their capacity for restraining oxidation reactions manifests itself only when

these reactions are catalyzed (accelerated) by heavy metals. The supposition has been expressed [see Note 2] that, in the oxidation reactions evoked by radiation, a large catalytic role is played by iron. This catalysis apparently does not determine the entire primary radiation effect, but it unquestionably plays a part in the primary processes of radiation contamination. This is graphically illustrated by a prophylactic experiment. When traces of iron ions are added to lipids, cyano- compounds manifest a protective effect and act on these models as an antioxidant. [Note 1. See the collected works of the UFAN [Ural'skiy Filial Akademii Nauk -- Urals Branch of the (USSR) Academy of Sciences] Biophysics Laboratory; Biofizika, Vol. 2, No. 1, 1957.) (Note 2. See Voprosy radio-biologii [Problems of Radiobiology], Vol. 2, 1957.)

Physiological Protection

Z. M. Bacq long ago discovered that some aminos which do not act as antioxidants, or do so to but a small degree, exert a prophylactic effect. Among such substances are histamine, phenyl ethylamine, adrenalin and, in particular, tryptamine [ ] and its derivative sulfuthonine [ ]. Although these substances manifest no sharply defined antioxidant properties with respect to a lipid model, they exert a fair prophylactic effect on higher animals. Their action is not distinguished by that universality which characterizes the protective substances possessing an antioxidant function; they are ineffective with respect to the protection of unicellular organisms. On the basis of a study of the protective-action mechanism of tryptamine [ ] and sulfothonine [ ], researchers came to the conclusion, already several years ago, that their protective effect is connected with another mechanism. Both compounds suppress cellular respiration, particularly in the cells of the brain and of the respiratory center, as a result of which oxygen impoverishment takes place in the tissues. This has been satisfactorily proven by experiments wherein, simultaneously with the introduction of tryptamine [ ] and other substances into the organism of animals, the quantity of oxygen in their tissues was determined by the polarographic method. It was established that, under the action of these substances, oxygen content in the tissues is reduced, this reduction being of the same order as in experiments where protection against radiation contamination was brought about through a reduction of oxygen pressure in the inhaled air. Such a type

of protection can in distinction from the chemical, be called physiological protection. Its ultimate mechanism is also reducible to the suppression of oxidizing processes.

In spite of the fact that a large number of protective preparations is being tested in various laboratories the world over, only few of them show any promise. This is explained by the fact that, in addition to the chemical properties, a substantial part is also played by the physiochemical conditions. In the first place, cell-wall permeability serves as a limiting factor. Many compounds which, according to their chemical properties, should manifest a prophylactic effect, turn out to be ineffective in connection with the fact that either they do not penetrate into the cells at all, or penetrate at a very slow rate. An attempt, for instance, to increase the number of amino groups leads to an increase in the polarity of the corresponding molecules which, as is well known, reduces, the capacity of molecules to penetrate into the cells. The second limiting condition is the toxicity of these compounds, which does not permit them to be introduced into the organism in sufficient quantity to afford protection. Finally, their stability is insufficient. Many protective substances, when introduced into higher animals, do not have time to penetrate into the cells but, breaking down, react with various substances and thereby lose their protective properties. For this reason, many substances which manifest a protective effect in experiments, for instance, with bacteria turn out to be inapplicable to higher animals.

As has already been indicated, prophylactic substances are effective only when introduced immediately prior to irradiation; employed already after irradiation and during the development of radiation sickness, they prove ineffective. Z. M. Bacq has been successful in obtaining a favorable effect with the introduction of large quantities of cysteine also in the hours most immediately following irradiation (however, he attributes it to the action of another mechanism). At later times, even the converse is noted, i.e., a negative effect of these substances, connected apparently with the fact that, after irradiation, secondary reactions develop that can be reinforced by these substances. It has recently been repeatedly noted that, soon after irradiation, animal tissues acquire the property of undergoing antolysis, i.e., of being broken down by tissue enzymes, at a very much more rapid rate than the tissues of normal animals. As is well known, the process of antolysis, being dependent on the action of proteolytic (i.e., those which break down proteins) cell enzymes, is activated by such compounds as cystein and glutathione which manifest a protective

effect in cases of radiation contamination. The unfavorable action and the absence of a positive effect upon the introduction of protective substances can, apparently, be explained by the fact that the protective substances and the lack of oxygen intensify the autolysis process, which plays a substantial part in the development of radiation contamination.

Although all the currently existing methods of protection are directed at suppression of the oxidation reactions brought about by radiation, there is reason to suppose that these reactions nevertheless do not serve as the sole primary cause of radiation contamination. It is possible that in the primary reaction between the substance of a living organism and radiation, other reactions originate as well, upon which antioxidants suppressing the chain reactions have no effect. An analysis of data obtained with the use of protective agents shows that the protective effect brought about by chemical agents does not provide absolute protection.

At the present time, chemists have synthesized very many different compounds which have a protective effect. The special attention of researchers is beginning to be drawn to those substances which, present in the cells of organisms in their normal condition, reduce their radiosensitivity. The sensitivity of organisms to radiation is, as is well known, subject to strong fluctuations. It has, for instance, been established that among microbes of the same species, the radiosensitivity of individual breeds [cultures?] can vary many hundredfold. For instance, it has been shown that for the pigmented forms of one of the bacteria, the lethal dose amounted to 3,000,000 r, and for the unpigmented, to but 40,000 r. The radiation resistance of many organisms is connected, in addition to the metabolic characteristics, with the presence in their cells of substances capable of providing chemical protection. The attention of researchers is being drawn in this direction by such substances as some nucleinic-acid derivatives, fatty substances and pigments, entering into the composition of cells.

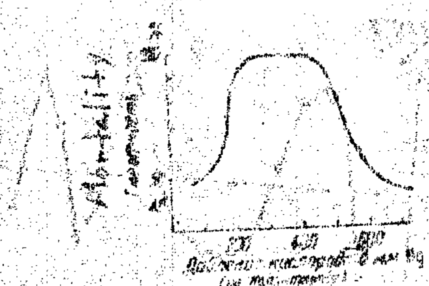
Study of the rules governing the mortality of organisms, in the period following irradiation, shows that this mortality is not uniformly distributed, but has peaks corresponding to specific periods (Figure 2). When subjected to the action of protective substances, the distribution picture for such mortality "peaks" changes; however, in some of the peaks no influence is exerted on mortality by the protective substances, there "peaks of destruction" reflect the primary reactions, and the

data presented above can serve as proof of the fact that not all these reactions can be suppressed by the prophylactic substances known to us at the present time.

* * *

The problem of searching out full-valued chemical compounds which could inhibit the primary reactions of radiation contamination, is a very pressing one. The existing difficulties are linked to the fact that the complex of those radiochemical reactions, the so-called primary reactions, which arise under the influence of radiation in various biochemical component elements of cells and tissues, has not yet been determined with sufficient clarity. In these reactions, which are accompanied by high ion yields, the principal part is played by active intermediate products -- radicals and peroxides of various types. To make possible the inhibition of the processes in their initial stage, it is necessary to know what these products are, and this requires the joint participation, in the research, of chemists, physicist, and biologists.

FIGURE APPENDIX



Oxygen pressure in mm Hg
(according to Kolontarov)

Figure 1. Mortality curves of yeast, depending on oxygen concentration (according to Kolontarov).

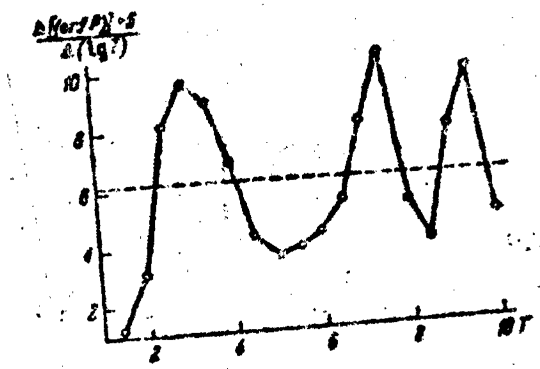


Figure 2. Peaks of mouse mortality with a radiation dose of 1,000 r of - rays. Depicted is the increment of mortality according to the logarithm of time. T - time after irradiation (in days, according to Luchnik).

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